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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/997,573
Filing Date: November 15, 2001
Appellant(s): ASHKENAZI ET AL.

Ginger R. Dreger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 13 January 2006 appealing from the Office action mailed 24 November 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/944,929 - filed 31 August 2001

09/989,729 - filed 19 November 2001

09/993,748 - filed 14 November 2001

09/906,742 - filed 16 July 2001

09/904,011 - filed 11 July 2001

09/904,485 - filed 13 July 2001

09/989,725 - filed 20 November 2001

The 09/989,725 application is directly related to the instant appeal because the claims are directed to antibodies that bind to the polypeptide PRO1375, said polypeptide being claimed in the instant application. The other applications are related to the instant appeal because the central issue of the appeal is whether utility is demonstrated by activity in the MLR (mixed lymphocyte reaction) assay. Because the issue in question is the same, these appeals may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. This list is not exhaustive, but are at least those appeals known to the Examiner in

which the central issue of the appeal is whether utility is demonstrated by activity in the MLR (mixed lymphocyte reaction) assay.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is essentially correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

A substantially correct copy of appealed claims 25-28 and 35-40 appears on pages 30-32 of the Appendix to the appellant's brief 0-1998 (newly cited by

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

a) Kahan, Current Opinion in Immunology. 4: 553-560, 1992.

b) Piccotti et al., Transplantation, 67 (11): 1453-1460, 1999.

c) Campo, et al., Biol. Trace Element Res., 79: 15-22, 2001.

d) Nishioka et al. Journal ofLeukocyte Biology, Vol.73, pages 621-219, 2003.

e) Current Protocols in Immunology, Vo.1, Richard Coico, Series Ed, John Wiley & Sons, Inc. 1991, Unit 3.12.

f) Gubler et al., PNAS 88 : 4143-4147, 1991. (cited by Appellant)

g) Peterson et al., J. Clinical Oncology 21412) : 2342-2348, 2003. (cited by Appellant)

h) Thurner et al., J. Experimental Medicine, 190(11) : 1669-1678, 1999. (cited by Appellant)

i) Steinman et al. Drug News Perspect. 13(10): 581-586, 2000. (cited by Appellant)

j) US Patent No. 5,817,306 HASKILL et al. 10-1998 (newly cited by Examiner)

Priority:

The grounds of rejection in the instant application are a direct result of the determination of priority for the claimed subject matter. Appellant asserts priority of the instant application to Provisional Application 60/144,758, filed 20 July 1999. However, priority has not been granted to this earlier application. Based on the invention given by Appellant and an inspection of the patent applications, the Examiner has concluded that the subject matter defined in this application is not supported by the disclosure 60/144,758, filed 07/20/1999 because the claimed subject matter does not have utility/enablement for the asserted utility of those applications (i.e. asserted utility of stimulating the immune system).

Accordingly, the subject matter defined in claims 119-127, 129-131 is afforded an effective filing date of 11/15/2001, which is the filing date of the current application.

(9a) Grounds of Rejection

Claim Rejections - 35 U.S.C. §101, §112, first paragraph :

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following grounds of rejection are applicable to the appealed claims:

Claims 119-127 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 119-127 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantially asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Appellant asserts that the specification shows that PRO1375 stimulates an immune response and induces inflammation in the skin vascular permeability assay. However, this assay appears to be nothing more than a toxicity test and does not provide a real-world, readily available use. It should be made clear that Appellant is not appealing this assertion. Appellant's ground of appeal deals with whether the MLR

assay (Example 151) satisfies the utility requirement set forth in 35 U.S.C §101 or "how to use" prong of the enablement under 35 U.S.C §112.

The instant specification discloses that the claimed protein (PRO1375 - SEQ ID NO:418) tested positive in the MLR assay wherein "positive increases over control are considered positive" (see pages 208-209 of the specification).

It was previously asserted by the Examiner that insufficient evidence was provided to support the position that the MLR assay was an art recognized in vitro assay that was predictive of general immune responses in vivo. Several references were cited during the prosecution of the instant application which demonstrated either a showing that the results of the MLR assay were consistent with in vivo activity or were inconsistent with in vivo activity. Upon review of the prior art, the Examiner found a patent that states "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules in vitro that are useful for treating graft versus host disease. The results obtained from these assays are generally predictive of their in vivo effectiveness." (See column 12, lines 36-41 of US Patent No. 5,817,306). Therefore, it is conceded that the MLR assay is art recognized for identifying molecules which suppress an immune response. However, another basis for rejecting the claims for lack of utility has been the lack of support in the specification for the assertion that the polypeptide of the instant claims actually stimulates the proliferation T- lympohcytes. In Example 151 on page 525, it is stated that "positive increases over control are considered positive however,

increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein", (see page 525, lines 29-33). The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that a certain protein tested positive and the statement that "any value more than control indicates an stimulatory effect for the test protein'. If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth regarding the nature of the MLR assay and how those skilled in the art use this assay and what kind of determinations can be made about compounds which are tested in this assay. The MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data

whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this should control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion of the specification. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay and therefore, the polypeptide in question may not alter the proliferation of stimulated T- lymphocytes to a significant extent. In conclusion, the results of the MLC (a.k.a. MLR) assay as disclosed in the specification for the polypeptide PRO1375 do not support a specific and substantial utility for the claimed invention because one of ordinary skill in the art would not conclude that a molecule which tested positive in the assay of the specification wherein any increases over control is considered to be a positive result" would be useful as a molecule for therapeutically stimulating an immune response in an individual (asserted use). There is insufficient data presented, as well as insufficient controls used, to conclude anything regarding the ability of the claimed polypeptide to be used in a substantial way to therapeutically inhibit the immune response of an individual, and further experimentation would be required to use the invention in this manner.

(9b) Grounds of Rejection

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 119-123 are directed to a polypeptide having at least 80%, 85%, 90%, 95%, 99% sequence identity to a the polypeptide of SEQ ID NO: 418, wherein said polypeptide induces proliferation of T lymphocytes in a mixed lymphocyte reaction.

However, the specification teaches only the structure of the polypeptide of SEQ IDNO: 418. The specification does not teach functional or structural characteristics of all the claimed polypeptides. Claims 124-126 recite the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:418, however, the instant specification does not describe the structure of said extracelular domain. The description of one PRO polypeptide (SEQ ID NO: 418) is not adequate written description of an entire genus of functionally equivalent polypeptides. Therefore, the claims do not require that the claimed polypeptides possess any particular conserved structure, or other disclosed distinguishing feature to retain the desired biological activity. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional

characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity without any guidance as to which positions of the polypeptides would tolerate changes to retain the desired biological activity. There is not identification of any particular portion of the structure that must be conserved.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 418, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

(9c) Grounds of Rejection

Claim Rejections - 35 U.S.C. §102(b):

Claims 119-125, 129-131 stand rejected under U.S.C. § 102(b) as being anticipated by (WO 00/18904 June/2000), (WO 99/63088, September/1999), (WO 00/00610, June/2000), (WO 00/00506, June/2000). Claims 119-125, 127 and 129-138 stand rejected under 35 U.S.C § 102(a) as being anticipated by (EP 1130094, September/2001).

Each of references, WO 00/18904, WO 99/63088, WO 00/00610, WO 00/00506 and EP 1130094, discloses an isolated polypeptide that shares 100% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:418, recited in claims 119-125, 129-131 of the instant application. Regarding claim 129, it is understood that the deposited sequence encodes the polypeptide of SEQ ID NO:418, therefore, since the polypeptide disclosed by each of the above references shares 100% identity to the polypeptide of SEQ ID NO:418, these references also anticipate claim 129. With respect to claims 130 and 131, each of the cited references also

discloses a chimeric or fusion protein comprising its polypeptide and a heterologous polypeptide.

(10a) Response to Argument

Appellant argues, beginning at page 7 of the response, that the reference cited by the Examiner to show that there is no correlation between the ability to stimulate proliferation of lymphocytes in the MLR in vitro assay and that same ability in vivo, i.e Kahan et al., Piccotti et al., and Campo et al., are insufficient to make the prima facie case. However, as stated above, the disclosure of newly cited US Patent No. 5,817,306 establishes the state of the art at the time the invention was made that the results of the MLR assay are generally predictive of in vivo effects. Therefore, arguments directed to the correlation or predictive nature of the MLR assay are moot and will not be addressed further. However, arguments directed toward the disclosure of the specification and the conclusion that can be made from said disclosure will be addressed since they are critical to the holding of lack of utility for inhibition of T-lymphocyte proliferation by the claimed polypeptide.

Appellant states at page 5 of the response that the Declaration of Dr. Sherman Fong was submitted 5 August 2004. This declaration has been fully considered, but not found to be persuasive. Dr. Fong concludes "a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 180% over control, as specified in the present application, would be expected activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulation". In assessing the weight to be given expert testimony, the Examiner may properly consider, among other

things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See & parte Simnson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Inrl. Ltd. v. Lotus Develonment Corn., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paranon Podiatrv Lab.. Inc. v. KLM Lab., Inc., 948 F.2d 1 182, 25 USPQ2d 1561, (Fed. Cir.1993). In the instant situation, the nature of the fact sought to be established is whether or not the disclosure that PRO1375 tested "positive" in the MLR assay of Example 151 supports the assertion that it could be used to stimulate proliferation of T-lymphocytes and therefore, be used for therapeutic enhancement of the immune system. Dr. Fong's statement that the present invention has an activity of at least 180% is questioned because there is no data presented to support this conclusion. The specification may state that increases of greater than or equal to 180% are preferred, but there is no disclosure, in the specification or in any other source, that the alleged increase reported in the specification for the claimed protein was of any particular degree. The only conclusion that can be made from the evidence provided for the claimed protein of PRO1375 is that the increase was a value greater than control since this was the standard provided for determination of a positive increase. The significance of this conclusion can be questioned since proper assay controls, deemed essential in the art were not used and because the standard for determination of a positive response in the assay would not be accepted by those of skill in the art (statistical significance is the standard for evaluating therapeutic value of a compound). The expert has interest in the outcome of the case since Dr. Fong is

listed as an inventor and is employed by the assignee. Finally, tie expert refers to Gubler et al. as factual support for the conclusions in the declaration. However, Gubler et al. do not appear to indicate that a protein shown to stimulate T-cell proliferation in an MLR assay with an activity of at least 180% would be expected to have the type of activity as that exhibited by IL-12. Furthermore, Gubler et al. (as well as Peterson et al. and Thurner et al.) are silent to any activity possessed by the claimed protein. The Fong declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1375 protein has not been shown to therapeutically enhance the immune system. The specification merely demonstrates that the PRO1375 protein increases T-cell proliferation above control. It is not known whether this increase is significant or what the relative increase in proliferation is. In the absence of any of the above information, all that the specification does is present evidence that the PRO1375 protein may increase T-cell proliferation and invites the artisan to determine the significance of this increase and whether it is meaningful (i.e. useful for a therapeutic benefit). It remains that the specification is not sufficient to conclude anything about the nature of the activity of the PRO1375 protein. Based on consideration of the evidence as a whole, the finding of lack of utility based on the MLR assay of Example 151 is proper.

Appellant argues at page 7 of the Brief that the standard for utility is that it is "more likely than not" that the asserted utility is specific and substantial and that the Examiner "has misinterpreted the focus of the assay disclosed in the specification". Appellant's argument has been fully considered, but is not persuasive. The question of

whether the art recognizes the MLR assay as predictive of in vivo therapeutic value has been answered. However, the specification does not support the conclusion that the claimed protein (PRO1375) stimulates proliferation of T-lymphocytes such that it would have therapeutic application for enhancing the immune response. As pointed out previously, no data is presented and the statement that proliferation was greater than control is not sufficient for concluding that the claimed protein would be useful for a therapeutic application, which is the asserted utility based on this assay. The assay relied upon in the instant specification is deficient in that proper art-recognized controls are not present, measured values of stimulation are not present, variability is not disclosed, statistical significance is not disclosed, such that an independent evaluation and conclusion cannot be made. One skilled in the art would have to do further research to determine whether or not the increase in T-cell proliferation by PRO1375 polypeptide in the MLR assay is real and significant, and therefore, support the asserted use for therapeutic enhancement of immune response.

Such further research requirements make it clear that the asserted utility is not yet in currently available form, ie-, it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in Brenner F. Mansoni 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "lulnless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "lilt is not a reward for the search, but

compensation for its successful conclusion."

At pages 6-7 of the Brief, Appellant's arguments regarding enablement appear to depend from the arguments regarding use of the claimed protein for stimulating an immune response. These arguments have been addressed above, and therefore, do not require repeating.

Appellant argues at page 9 of the Brief that the instant application claims priority to an earlier filed application (60/144,758, filed 20 July 1999) and that they are entitled to benefit to this earlier filed application based on the disclose that PRO1375 tested positive in the MLR assay. As pointed out in the grounds of the rejection, this is an issue to be addressed in this Appeal. If the disclosure in the specification is deemed sufficient to provide utility for the claimed invention based on the asserted use for therapeutic stimulation of an immune response, then Appellant is entitled to the effective filing date of the 60/144,758 application.

However, priority has been denied because the disclosure has been found insufficient to establish this utility for the claimed invention.

At pages 10-13, Appellant reviews case law pertaining to the legal standard for patentable utility, with which the Examiner does not take issue. At page 13, Appellant asserts that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (MPEP § 2170.01).

The argument has been fully considered, but is not persuasive. MPEP §2170.01 also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." In the instant situation, further research would be required to reasonably confirm that the claimed protein stimulates T-cell proliferation to a degree that it would be useful therapeutically for stimulating an immune response, which is the asserted utility in the specification.

Appellant states at page 14 of the Brief "[t]he positive result for PRO1375 in the MLR assay, described in Example 151, of the specification, demonstrates that PRO1375 is active as a stimulator of the proliferation of stimulated T-lymphocytes".

Appellant's assertion is noted, but the facts of record and the disclosure of the specification do not support this conclusion. As pointed out previously, the specification indicates that "positive increases over control are considered positive", yet art recognized controls, which are considered to be necessary for determining a meaningful result, are not present. The specification fails to include any values which were obtained from the assay, so the results of the assay cannot be independently evaluated. If the degree of stimulation is greater than the control, but within the variability of the assay, then one of ordinary skill in the art would not conclude that the protein tested is a stimulator of T-cell proliferation, yet the specification would arrive at this conclusion. In order to be useful in the manner asserted in the specification (i.e. therapeutic enhancement of an immune response), the degree of stimulation of T-cell proliferation must be meaningful. One of ordinary skill in the art would usually evaluate

this by observing a statistically significant increase in T-cell proliferation over baseline. However, based on the limited disclosure in the instant specification, no conclusions can be made as to the activity of the claimed protein in this assay because proper controls are not provided and there is no data presented to evaluate. Therefore, further research would be required to reasonably confirm the asserted utility based on the MLR assay of Example 151.

Appellant's statements and arguments (pages 12-14) directed to use of the MLR to evaluate compounds for use as immunomodulators is noted. However, in view of the Examiner's concession that the MLR is an art accepted assay for this purpose, these arguments are moot.

Appellant again refers to the Declaration of Dr. Fong at pages 14-15 of the Brief. As stated previously, the Declaration has been fully considered but is not persuasive. Appellant asserts that the "specification clearly discloses that PRO1375 tested positive inthe MLR assay" and that the "Fong Declaration reinforces the teachings of the specification that a PRO polypeptide with an activity in the MLR assay of at least 180% of the control is expected to have the type of activity exhibited by IL-12, and would therefore find practical utility as an immune stimulant" (see page 15 of the Brief).

First, the statement that PRO1375 tested positive in the MLR assay is addressed above. The standard set forth in the specification that "positive increases over control are considered positive" is neither art accepted nor indicative of a meaningful increase in T-cell proliferation. Lacking proper controls and no data, the observation that PRO1375 tested "positive" is meaningless. All assays have variability and the observed

increase over control may be natural variation in the assay, and therefore, not an indication of an immunostimulatory. effect. Secondly, there is no disclosure that the PRO1375 protein of the instant invention has an activity in the MLR assay of at least 180%, therefore, no conclusions regarding it's activity can be made and one would not conclude that it would have practical utility as an immune stimulant. The Declaration of Dr. Fong is not specific to the claimed protein, PRO1375. The Declaration provides no data related to the claimed protein, PRO1375. Furthermore, the opinion of Dr. Fong that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12" is not supported by any facts or evidence of record. The references cited do not support this opinion and it is not clear how Dr. Fong arrived at this conclusion. There is no evidence of record which correlates an activity of at least 180% of control as predictive of an activity of IL-12 and there is no comparison of the claimed invention with IL-12. One of ordinary skill in the art would not conclude that the claimed protein has the activity of IL-12 because there is absolutely no data provided to support such an assertion. Therefore, the Declaration is not persuasive to overcome the holding of a lack of utility for the claimed invention based on the MLR assay. Appellant's arguments spanning page 16-25 are directed to use of the MLR to evaluate compounds for use as immunomodulators is noted. However, in view of the Examiner's concession that the MLR is an art accepted assay for this purpose, these arguments are moot. Appellant cites case law concerning the Examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be

considered. Appellant also points to the utility guidelines as directing the Examiner to accept an opinion from an expert. Appellant points to the statement in the Fong declaration that it is Dr. Fong's considered scientific opinion that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant". At page 24 Appellant argues that Nishioka et al reference provides supportive evidence for the Appellant's position that the art as a whole recognizes the MLR assay is in fact a widely used in vitro assay for identifying immunomodualtory compounds.
The Examiner has conceded the fact that the MLR assay is art recognized for identifying molecules which suppress an immune response, (See column 12, lines 36-41 of US Patent No. 5,817,306). However, another basis for rejecting the claims for lack of utility has been the lack of support in the specification for the assertion that the polypeptide of the instant claims actually stimulates the proliferation T- lympohcytes.

Appellant argues at page 25 of the Brief that the claims are enabled for the same reasons as provided for utility. However, since the arguments were not persuasive for Supporting utility, they are also not persuasive for supporting enablement. Because the claimed invention does not have utility for therapeutic enhancement of an immune response, and because the specification does not support the conclusion that PRO1375 stimulates T-lymphocytes based on an unreasonable standard for assessing activity and lack of proper experimental controls, the claims are also not enabled for protein

variants that stimulate proliferation of T-lymphocytes. Appellant argues that one skilled in the art could test whether a variant PRO1375 polypeptide is capable of stimulating proliferation of T-lymphocytes.

This argument has been considered but it is not persuasive. The specification has not provided sufficient evidence to support the assertion that the claimed invention is capable of stimulating proliferation of T-lymphocytes. Therefore, the claimed invention does not have utility for stimulating proliferation of T-lymphocytes for the reasons provided above, and likewise, the claims are not enabled for this use. Accordingly, since the PRO1375 protein is not enabled, the variants as well are not enabled.

(10b) Response to Argument

At pages 28-30, Appellant argues that claims 119-127, 129-131 recite the functional limitation that the polypeptide induces proliferation of stimulated T lymphocyte reaction, and that the skilled artisan could easily identify whether a variant falls with in the parameters of the invention. Appellant refers to the arguments and information presented in response to the rejections for lack of utility and enablement. Appellant submits that the specification provides ample written description for the claimed polypeptide in Example 151, where methods of detecting and quantifying amplification in tumors cell lines are described. Appellant urges that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO:418 and that the Examiner has acknowledged that the polypeptide comprising SEQ ID NO:418 meets the written description provision of 35 U.S.C §112, first paragraph. Thus, Appellant submits that the genus of polypeptide with at least 80% sequence

identity to SEQ ID NO:418, which possess the recited functional property of h would meet the requirement of written description provision of 35 U.S.C §112, first paragraph. Appellant also points to the specification's disclosure of methods for the determination of percent identity, and assays for identification of nucleic acids and for support of the functional limitation in the claims. Appellant urges that the skilled artisan can readily test native polypeptide sequences for identity and whether or not the polypeptide induces proliferation of stimulated T lymphocyte reaction.

This argument has been fully considered but is not found to be persuasive. Appellant's discussion of the legal test for written description is acknowledged. However, the specification fails to disclose on single variant that retains the recited functional limitation. As pointed out previously, the specification indicates that "positive increases over control are considered positive", yet art recognized controls, which are considered to be necessary for determining a meaningful result, are not present. The specification fails to include any values which were obtained from the assay, so the results of the assay cannot be independently evaluated. If the degree of stimulation is greater than the control, but within the variability of the assay, then one of ordinary skill in the art would not conclude that the protein tested is a stimulator of T-cell proliferation, yet the specification would arrive at this conclusion. In order to be useful in the manner asserted in the specification (i.e. therapeutic enhancement of an immune response), the degree of stimulation of T-cell proliferation must be meaningful. One of ordinary skill in the art would usually evaluate

this by observing a statistically significant increase in T-cell proliferation over baseline. However, based on the limited disclosure in the instant specification, no conclusions can be made as to the activity of the claimed protein in this assay because proper controls are not provided and there is no data presented to evaluate. Therefore, further research would be required to reasonably confirm the asserted utility based on the MLR assay of Example 151. It might be obvious to one of ordinary skill in the art to determine whether a variant falls with in the parameters of the invention. However, the written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one is in possession of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. Therefore, only the isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 418, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

(10c) Response to Argument

Appellant argues the rejection of the claims based on the prior art of (WO 00/18904 June/2000), (WO 99/63088, September/1999), (WO 00/00610, June/2000), (WO 00/00506, June/2000). (EP 1130094, September/2001) at pages 31-32.

Essentially, Appellant contends that priority to provisional application 60/144,758 should be granted because the MLR assay was first disclosed in this application, and the MLR assay supports utility and meets the requirements of 35 U.S.C. 112 for the subject matter of the instant claims. However, because the arguments regarding utility

based on this assay have not been found persuasive for the reasons provided above, the instant application is not entitled to benefit of this earlier filed application. Therefore, the effective filing date is the filing date of current application, which is 11/15/2001.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Fozia Hamud

Conferees:

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

EILEEN B. O'HARA
PRIMARY EXAMINER